# TESTING OF ANTIMICROBIAL ACTIVITY OF PRESERVATIVES FOR DENTAL GELS DEVELOPMENT

**Maslii Yu. S., Ruban O. A, Kaliuzhnaia O. S., Khokhlenkova N. V**
**National University of Pharmacy**
**julia.masliy@gmail.com**

## Introduction

Oral cavity diseases are the most common diseases in the world and aren't only a medical but also social problem. To date, among patients of different age groups there is a high incidence of periodontal tissue and mucous membranes diseases, which worsen the health of other organs and reduce the quality of socio-psychological life [1, 2]. The list of complications caused by periodontal diseases, first of all, includes inflammatory processes of the maxillofacial area, digestive disorders, compromised resistance to infectious and other agents [3]. This, in turn, requires appropriate treatment, which is mainly based on the use of topical drugs [4, 5].

According to the analysis of scientific literature, the most common topical dosage form in dental practice is gel, which combines the properties of solid and liquid forms, and therefore is easy to use and effective in applications [6-8].

At the Industrial Technology of Drugs Department of National University of Pharmacy, two dental gels are being developed under the name "Cholident" and "Lysostom", which contain carbopol and hydroxyethylcellulose as gelling agents respectively, and purified water as a solvent. It is known that hydrophilic bases provide a uniform distribution of the gel on oral mucosa and contribute to effective therapeutic effect of active pharmaceutical ingredients (API), however, at the same time, they are prone to microbial contamination [9]. In addition, the developed drugs contain API of natural origin, which are also a favorable environment for the multiplying of microorganisms [10].

Previous studies showed that freshly prepared gels satisfied the requirements of SPhU for microbiological purity [15]. However contamination of the samples by test-microorganisms caused their intensive growth, which proved necessity for introduction of antimicrobial preservatives into the gels. These adjuvants prolong the shelf life of pharmaceutical products, increase their resistance to spoilage after opening the package, especially in the case of using multi-dose containers, and, accordingly, prevent infection of the patient [12-14].

Therefore, the **aim** of this work was selection of effective antimicrobial preservatives in rational concentrations for the composition of dental gels "Cholident" and "Lysostom".

## Materials & methods

The composition and characteristics of the components of gels "Cholident" and "Lysostom" are presented in Table 1.

**Table 1. The composition of dental gels are being developed**

| Name of ingredient | Manufacturer | Role in drug composition |
|---|---|---|
| *Gel "Cholident"* | | |
| Tincture "Phytodent" | PJSC «CPP Chervona zirka», Ukraine | API |
| Choline salicylate 80 % | Basf Pharma, Switzerland | API |
| Lidocaine hydrochloride | Societa Italiana Medicinali Scandicci, Italy | API |
| Carbopol Polacril® 40P | Amedeo Brasca & C. Srl, Italy | gelling agent |
| Sodium hydroxide (10 % solution ) | Chemical reagents, Ukraine | neutralizer |
| OraRez® W-100L16 | BOAI, China | mucosal adhesive |
| Purified water | | solvent |
| *Gel "Lysostom"* | | |
| Lysozyme hydrochloride | Bouwhuis Enthoven B.V., Netherlands | API |
| Hydroxyethylcellulose Natrosol™ 250HHX | Ashland, Holland | gelling agent |
| Glycerol | BASF, Germany | hydrophilic non-aqueous solvent (plasticizer, humidifier, adhesive) |
| Purified water | | solvent |

The following ingredients were selected as preservatives in the gels are being developed: benzoic acid, sodium benzoate, sorbic acid, potassium sorbate, methyl parahydroxybenzoate (nipagin), propyl parahydroxybenzoate (nipazol). The concentration of preservatives for all gel samples was 0.1 % and 0.2 % [12-14].

The implantation of selected preservatives in composition of the gel "Cholident" was carried out taking into account their solubility: benzoic acid, sorbic acid and nipagin : nipazol were dissolved in alcohol tincture "Phytodent"; potassium sorbate and sodium benzoate – in purified water. Nipagin and nipazol were used in a ratio of 3:1 to expand the antimicrobial action on both bacteria and fungi.

For the preparation of gel "Lysostom", potassium

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sorbate and sodium benzoate were dissolved in purified water at room a temperature, and nipagin – at a temperature of 80 °C. Adding of benzoic and sorbic acids to the gel caused denaturation of lysozyme hydrochloride and forming of a white precipitate, so these preservatives were excluded from the experiment. Nipazol due to its very poor solubility in water [12, 14] was also not used.

The selection of preservative for the composition of dental gels "Cholident" and "Lysostom" was based on the study of its antimicrobial activity. Preservatives effectiveness tests were carried out according to the method of SPhU 2.3, Ch. 5.1.3 [15].

In order to test the effectiveness of selected antimicrobial preservatives, each container with a gel sample was inoculated by freshly prepared suspension with one of the test-microorganisms, while providing a microbial load of $10^5$ CFU to $10^6$ CFU in 1 ml of the sample, stirred thoroughly for even distribution in the gel sample and stored at temperature 20-25 °C in a dark place. Immediately after inoculation and at regular intervals (drugs for oral administration after 14 and 28 days), 1 ml was taken from each sample and a number of viable microorganisms was determined by surface sowing on dishes. The criterion for preservative effectiveness evaluation was a reduction of the number of viable test-microorganisms in the drug for a certain period of time after its contamination. According to the requirements of SPhU, the logarithm of decrease in the number of viable bacterial cells after 14 days should be at least three with no further increase in quantity of microorganisms; the logarithm of decrease in the number of viable fungal cells after 14 days should be at least one, in the future the number of viable fungal cells shouldn't increase [15].

As a bacterial test-culture *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Candida albicans* ATCC 10231, *Aspergillus brasiliensis* ATCC 16404 and *Escherichia coli* ATCC 8739 (last one is recommended in studies for oral drugs) were used; inoculum preparation was performed according to SPhU [15].

According to the requirements of SPhU, the sterility test of culture medium and solvent: growth properties of culture medium (soy-casein culture medium – for bacterial cells growth and Saburo-dextrose medium without antibiotics – for fungal cells) and suitability test of methods for determining the total number of cells were performed.

As a control in determining the growth qualities of the culture medium was a standard medium with pre-established growth properties, which correctly manifests the quantitative and qualitative growth of microorganisms (morphology of colonies). Culture medium satisfied the growth properties and sterility test according to SPhU requirements [11], and the test-microorganisms met taxonomic characteristics – morphology of the colonies on the medium and morphology of cells under microscopy were typical for the strain.

Suitability of the method for determining the total number of viable cells was carried out by comparing the number of test-microorganisms of the test drug and control inoculations. The antimicrobial activity of the drug was eliminated by dilution. Suitability of the method for determining the total viable microorganisms was tested in the drug samples diluted 1:10 by solvent buffer solution of sodium chloride and peptone pH = 7.0 with 5 % polysorbate-80, 0.5 % lecithin and 0.1 % histidine hydrochloride. The method of surface inoculation with samples diluted 1:10 and using a typical neutralizing solvent is suitable for determining the number of microorganisms in the samples and can be used for antimicrobial drug's effectiveness test.

**Results & discussions**

Drugs or their individual components can inhibit the growth of contaminating microorganisms. Determining the presence or absence of antimicrobial action and its neutralization is an important part of the preparatory work before the study of the drug [16]. Previous studies have shown moderate antibacterial and fungicidal activity for "Cholident" gel [17] and for "Lysostom" gel [18], but even if no increase in the number of viable cells was observed during the development period, during storage gel samples without preservatives didn't meet the requirements of microbiological purity of SPhU criteria for oral aqueous preparations [15]. Therefore, in order to effectively protect the drug from microbial contamination during storage and use, samples of gels with preservatives were prepared.

It's known that selection of preservatives and their dosage depends on: degree of bacterial contamination and qualitative composition of the microflora; conditions of production and storage; chemical composition of the product and its physicochemical properties; expected shelf life. In addition, the development of dental gels should take into account compatibility of the preservative with API, potential for oral use and its safety [19].

Results of the effectiveness study of selected antimicrobial preservatives in the gel "Lysostom" are presented in Table 2.

**Table 2. Results of the effectiveness of antimicrobial preservatives in the gel "Lysostom"**

| Test-microorganisms | Preservative concentration,% | lg of number of viable microorganisms immediately after inoculation, lg CFU/ml | lg reduction of viable microorganisms number, lg CFU/ml (SPhU requirements 2.3 / results obtained) | |
|---|---|---|---|---|
| | | | 14 days | 28 days |
| Nipagin | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.28 | 3/3.22 | NI/ND |
| | 0.2 | 5.34 | 3/ND | NI/ND |

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| | | | | |
|---|---|---|---|---|
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.58 | 3/3.68 | NI/ND |
| | 0.2 | 5.51 | 3/3.95 | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.60 | 3/ND | NI/ND |
| | 0.2 | 5.58 | 3/ND | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.58 | 1/3.04 | NI/ND |
| | 0.2 | 5.58 | 1/4.18 | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.58 | 1/2.84 | NI/ND |
| | 0.2 | 5.65 | 1/ND | NI/ND |
| Sodium benzoate | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.32 | 3/ND | NI/ND |
| | 0.2 | 5.28 | 3/ND | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.54 | 3/3.84 | NI/ND |
| | 0.2 | 5.48 | 3/ND | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.60 | 3/ND | NI/ND |
| | 0.2 | 5.56 | 3/ND | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.57 | 1/3.57 | NI/ND |
| | 0.2 | 5.60 | 1/ND | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.65 | 1/3.20 | NI/ND |
| | 0.2 | 5.61 | 1/ND | NI/ND |
| Potassium sorbate | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.30 | 3/3.12 | NI/ND |
| | 0.2 | 5.36 | 3/3.30 | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.57 | 3/3.55 | NI/ND |
| | 0.2 | 5.44 | 3/3.71 | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.58 | 3/3.18 | NI/ND |
| | 0.2 | 5.52 | 3/3.46 | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.60 | 1/2.41 | NI/ND |
| | 0.2 | 5.62 | 1/4.14 | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.60 | 1/2.60 | NI/ND |
| | 0.2 | 5.62 | 1/ND | NI/ND |

Notes: NI – no increase in the number of microorganisms compared to the number of viable microorganisms at the previous control point; ND – no viable cells of microorganisms were detected in the experiment.

The results presented in Table 2, indicate that after 14 days of storage of inoculated samples of gel "Lysostom" with preservative nipagin a lg reduction of viable microorganisms was more than 3.0 and was 3.22 for *Staphylococcus aureus* at a concentration 0.1 %, 3.68 for *Pseudomonas aeruginosa;* for *Escherichia coli* – viable bacterial microorganisms were not detected; at a concentration of 0.2 % viable cells were not registered for *Staphylococcus aureus* and *Escherichia coli,* and for *Pseudomonas aeruginosa lg* was equal to 3.95. For *Candida albicans* cells on day 14, the lg reduction of bacterial cells number in samples with nipagin 0.1 % was 3.04 (minimum according to requirements – 1.0), nipagin 0.2 % – 4.18. For culture of *Aspergillus brasiliensis* on day 14 with nipagin 0.1 % lg reduction was 2.84, however, in samples of gel with nipagin 0.2 % fungal cells were not detected. On day 28, viable bacterial and fungal cells were not detected in gel samples with a concentration of nipagin 0.1 % and 0.2 %.

For samples of "Lysostom" gel with preservative sodium benzoate 0.1 % and 0.2 % after 14 days of storage *Staphylococcus aureus* and *Escherichia coli* were not registered in any case, and lg reduction in number of bacteria *Pseudomonas aeruginosa* was 3.84 at a concentration of 0.1 %, and bacterial cells were not detected at 0.2 %. As of fungi colonies, in 14 days lg reduction of *Candida albicans* was 3.57 with 0.1 % sodium benzoate and no bacterial cells were found with concentration of preservative 0.2 %. A similar trend was observed for the fungus *Aspergillus brasiliensis*: at 0.1 % lg reduction was 3.20, and at 0.2 % – no microorganisms were detected. On the 28th day of the experiment, the cells of the test-microorganisms were not detected.

Based on the results of Table 2, samples of "Lysostom" gel with potassium sorbate in the amount of 0.1 % and 0.2 % also showed antimicrobial activity against test-microorganisms. Thus, on the 14th day lg reduction of bacterial cells number *Staphylococcus aureus* was 3.12 (potassium sorbate 0.1%) and 3.30 (potassium sorbate

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0.2 %), *Pseudomonas aeruginosa* – 3.55 (potassium sorbate 0.1 %) and 3.71 (potassium sorbate 0.2 %), *Escherichia coli* – 3.18 (potassium sorbate 0.1 %) and 3.46 (potassium sorbate 0.2 %), which exceeds the requirements of SPhU. For fungi, the results were: lg reduction of *Candida albicans* cells was 2.41 and 4.14, respectively, at concentrations of 0.1 % and 0.2 % of potassium sorbate in the gel sample, and for *Aspergillus brasiliensis* – 2.60 at a concentration of 0.1 % and were not detected at 0.2 % of potassium sorbate. On the 28th day of the experiment, cells of the test-microorganisms were not detected. Thus, the effectiveness of the preservative potassium sorbate in both concentrations in composition of the gel "Lysostom" meets the requirements of SPhU.

Summarizing the results of Table 2 for dental gel "Lysostom" with preservatives nipagin, sodium benzoate, potassium sorbate, it could be noted that the obtained data satisfy the requirements of SPhU for oral drugs. Among the preservatives listed above, sodium benzoate at a concentration of 0.2 % had the highest antimicrobial activity.

In the Table 3 presented the results of study of selected antimicrobial preservatives effectiveness in the composition of the gel "Cholident".

**Table 3. Results of the effectiveness of antimicrobial preservatives in the gel "Cholident"**

| **Test-microorganisms** | **Preservative concentration,%** | **lg of number of viable microorganisms immediately after inoculation, lg CFU/ml** | **lg reduction of viable microorganisms number, lg CFU/ml (SPhU requirements 2.3 / results obtained)** | |
|---|---|---|---|---|
| | | | **14 days** | **28 days** |
| Nipagin : nipazol (3:1) | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.38 | 3/ND | NI/ND |
| | 0.2 | 5.36 | 3/ND | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.54 | 3/4.05 | NI/ND |
| | 0.2 | 5.58 | 3/4.18 | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.58 | 3/ND | NI/ND |
| | 0.2 | 5.60 | 3/ND | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.56 | 1/3.22 | NI/ND |
| | 0.2 | 5.62 | 1/ND | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.56 | 1/ND | NI/ND |
| | 0.2 | 5.60 | 1/ND | NI/ND |
| Sodium benzoate | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.18 | 3/3.52 | NI/ND |
| | 0.2 | 5.30 | 3/3.65 | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.54 | 3/3.86 | NI/ND |
| | 0.2 | 5.59 | 3/3.94 | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.58 | 3/ND | NI/ND |
| | 0.2 | 5.54 | 3/ND | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.61 | 1/3.08 | NI/ND |
| | 0.2 | 5.60 | 1/3.14 | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.65 | 1/2.00 | NI/ND |
| | 0.2 | 5.65 | 1/2.05 | NI/ND |
| Potassium sorbate | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.30 | 3/3.28 | NI/ND |
| | 0.2 | 5.32 | 3/3.37 | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.57 | 3/3.42 | NI/ND |
| | 0.2 | 5.59 | 3/3.48 | NI/ND |
| *Escherichia coli* | 0.1 | 5.54 | 3/3.59 | NI/ND |

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| | | | | |
|---|---|---|---|---|
| ATCC 8739 | 0.2 | 5.52 | 3/3.62 | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.62 | 1/2.95 | NI/ND |
| | 0.2 | 5.60 | 1/3.0 | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.60 | 1/1.83 | NI/ND |
| | 0.2 | 5.65 | 1/1.91 | NI/ND |
| Benzoic acid | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.26 | 3/3.56 | NI/ND |
| | 0.2 | 5.38 | 3/ND | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.56 | 3/3.86 | NI/ND |
| | 0.2 | 5.54 | 3/4.06 | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.60 | 3/ND | NI/ND |
| | 0.2 | 5.57 | 3/ND | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.60 | 1/3.11 | NI/ND |
| | 0.2 | 5.59 | 1/ND | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.57 | 1/2.09 | NI/ND |
| | 0.2 | 5.67 | 1/ND | NI/ND |
| Sorbic acid | | | | |
| *Staphylococcus aureus* ATCC 6538 | 0.1 | 5.34 | 3/3.49 | NI/ND |
| | 0.2 | 5.32 | 3/ND | NI/ND |
| *Pseudomonas aeruginosa* ATCC 9027 | 0.1 | 5.58 | 3/3.45 | NI/ND |
| | 0.2 | 5.58 | 3/3.88 | NI/ND |
| *Escherichia coli* ATCC 8739 | 0.1 | 5.56 | 3/3.61 | NI/ND |
| | 0.2 | 5.54 | 3/ND | NI/ND |
| *Candida albicans* ATCC 10231 | 0.1 | 5.59 | 1/3.0 | NI/ND |
| | 0.2 | 5.56 | 1/3.56 | NI/ND |
| *Aspergillus brasiliensis* ATCC 16404 | 0.1 | 5.59 | 1/1.89 | NI/ND |
| | 0.2 | 5.64 | 1/1.95 | NI/ND |

*Notes: NI – no increase in the number of microorganisms compared to the number of viable microorganisms at the previous control point; ND – no viable cells of microorganisms were detected in the experiment.*

Analyzing the obtained data presented in Table 3 of gel "Cholident" samples with a combination of preservatives nipagin : nipazol (3:1) in concentrations 0.1 % and 0.2 %, after 14 days of cultivation lg reduction of bacterial cells number was more than 3. *Staphylococcus aureus* and *Escherichia coli* cells were not detected at both concentrations, and for *Pseudomonas aeruginosa* lg reduction of cells number was 4.05 and 4.18 at 0.1 % and 0.2 % respectively. For fungi, this figure was greater than 1 and equal to 3.22 at a concentration 0.1 % for *Candida albicans* cells; at concentration 0.2 %, no microorganisms were detected, as for both concentrations in experiments with *Aspergillus brasiliensis*. On the 28th day of incubation, the test-microorganisms cells were not detected.

The results of study of gel "Cholident" with preservatives sodium benzoate and potassium benzoate proved that on the 14th day of storage of inoculated samples lg reduction of bacterial cells number was more than 3 and didn't grow significantly with an increase of preservatives concentration. Thus, for *Staphylococcus aureus* this indicator was 3.52 and 3.65 (sodium benzoate 0.1 % and 0.2 %, respectively), 3.28 and 3.37 (potassium sorbate 0.1 % and 0.2 %, respectively); for *Pseudomonas aeruginosa* – 3.86 and 3.94 (sodium benzoate 0.1 % and 0.2 %, respectively), 3.42 and 3.48 (potassium sorbate 0.1 % and 0.2 % respectively); for *Escherichia coli*, no viable cells were detected in the sodium benzoate samples, and for potassium sorbate, the lg reduction of cells quantity was 3.59 (potassium sorbate 0.1 %) and 3.62 (potassium sorbate 0.2 %). For the fungi *Candida albicans* lg reduction of the cells number was 3.08 and 3.14 in samples with sodium benzoate in concentrations of 0.1 % and 0.2%, respectively, and 2.95 and 3.00 in samples with potassium sorbate 0,1 % and 0.2 %, respectively. On the 28th day of storage of inoculated gel samples, test-microorganisms were not detected.

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A similar trend was observed for samples of gel "Cholident" with preservatives benzoic acid and sorbic acid – lg reduction of bacterial cells number was more than 3, fungi cells – over 1. On the 14th day of inoculation, this value for *Staphylococcus aureus* was 3.56 and 3.49 for samples with acids at a concentration 0.1 %; at a concentration of 0.2 % – cells were not detected. As of *Pseudomonas aeruginosa* – 3.86 and 4.06 (benzoic acid 0.1 % and 0.2 %, respectively), 3.45 and 3.88 (sorbic acid 0.1 % and 0.2 %, respectively). *Escherichia coli* was not detected in samples with benzoic acid; for sorbic acid in a concentration of 0.1 % this indicator was 3.61, and at 0.2 % – microorganisms were not detected. For fungi *Candida albicans* – 3.11 (benzoic acid 0.1 %); cells were not detected (benzoic acid 0.2 %) and 3.00 and 3.56 (sorbic acid 0.1 % and 0.2 %, respectively), and for *Aspergillus brasiliensis* – 2.09 (benzoic acid 0.1 %) and the cells were not detected (benzoic acid 0.2 %), 1.89 and 1.95 (sorbic acid 0.1 % and 0.2 %, respectively). On the 28th day of the experiment, the test-microorganisms cells were not detected.

Thus, the results of antimicrobial preservatives efficacy determination in the composition of the dental gel "Cholident" (Table 3) proved SPhU eligibility for all samples. The combination of nipagin : nipazol had the highest antimicrobial activity against all test-microorganisms, and, taking into account the requirements of economy and safety, their use at a concentration of 0.1 % will be sufficient.

**Conclusion**

1. Tests of the antimicrobial preservatives effectiveness in the experimental samples of dental gels "Lysostom" and "Cholident" proved that all the studied preservatives, namely sodium benzoate, potassium sorbate, nipagin and combination nipagin with nipazol, benzoic acid and sorbic acid, had high antimicrobial efficacy and met the requirements of SPhU for oral drugs.
2. Taking into account a slightly higher antimicrobial activity, the sodium benzoate at a concentration 0.2 % was selected as the most acceptable preservative for the gel "Lysostom". The combination nipagin : nipazol (3:1) was chosen as the most promising preservative for the gel "Cholident", which provided at a concentration 0.1 % stronger than other preservatives antimicrobial action. These measures will ensure the safety of the drugs during storage and use.

**Testing of antimicrobial activity of preservatives for dental gels development**

**Maslii Yu. S., Ruban O. A, Kaliuzhnaia O. S., Khokhlenkova N. V**

**Introduction.** Given the widespread prevalence of oral diseases, especially pathologies of periodontal tissues and mucous membranes, among the population of different ages and the needs of the pharmaceutical market in topical drugs for their treatment, the development of new domestic dental drugs is relevant. The most common topical dosage form in dental practice is gels, which are characterized by good distribution on the tissues of the oral cavity, prolonging effect and high bioavailability. At the Industrial Technology of Drugs Department of National University of Pharmacy, two dental gels are being developed under the name "Cholident" and "Lysostom". Previous studies showed that freshly prepared gels satisfied the requirements of SPhU for microbiological purity. However, contamination of the samples by test-microorganisms caused their intensive growth, which proved necessity for introduction of antimicrobial preservatives into the gels. These adjuvants prolong the shelf life of pharmaceutical products, increase their resistance to spoilage after opening the package, especially in the case of using multi-dose containers, and, accordingly, prevent infection of the patient. The **aim** of this work was selection of effective antimicrobial preservatives in rational concentrations for the composition of dental gels "Cholident" and "Lysostom". **Materials & methods.** The following ingredients were selected as preservatives in the gels are being developed: benzoic acid, sodium benzoate, sorbic acid, potassium sorbate, methyl parahydroxybenzoate (nipagin), propyl parahydroxybenzoate (nipazol). The concentration of preservatives for all gel samples was 0.1 % and 0.2 %. They have much lower toxicity than others, are harmless to humans even in large quantities and are permitted for the preservation of food and pharmaceutical products. The selection of preservative for the composition of dental gels "Cholident" and "Lysostom" was based on the study of its antimicrobial activity. Preservatives effectiveness tests were carried out according to the method of SPhU 2.3, Ch. 5.1.3. According to the requirements of SPhU, the sterility test of culture medium and solvent: growth properties of culture medium (soy-casein culture medium – for bacterial cells growth and Saburo-dextrose medium without antibiotics – for fungal cells) and suitability test of methods for determining the total number of cells were performed. **Results & discussion.** Tests have shown that for dental gel "Lysostom" with preservatives nipagin, sodium benzoate, potassium sorbate, it could be noted that the obtained data satisfy the requirements of SPhU for oral drugs. Among the preservatives listed above, sodium benzoate at a concentration of 0.2 % had the highest antimicrobial activity. The results of antimicrobial preservatives efficacy determination in the composition of the dental gel "Cholident" proved SPhU eligibility for all samples. The combination of nipagin : nipazol had the highest antimicrobial activity against all test-microorganisms, and, taking into account the requirements of economy and safety, their use at a concentration of 0.1 % will be sufficient. **Conclusion.** Thus, tests of the antimicrobial preservatives effectiveness in the experimental samples of dental gels "Lysostom" and "Cholident" proved that all the studied preservatives, namely sodium benzoate, potassium sorbate, nipagin and combination nipagin with nipazol, benzoic acid and sorbic acid, had high antimicrobial efficacy and met the requirements of SPhU for oral drugs. Taking into account a slightly higher antimicrobial activity, the sodium benzoate at a concentration 0.2 % was selected as the most acceptable preservative for the gel "Lysostom". The combination nipagin : nipazol (3:1)

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was chosen as the most promising preservative for the gel "Cholident", which provided at a concentration 0.1 % stronger than other preservatives antimicrobial action.

**Key words:** dental gel, preservative, microbiological studies, antimicrobial activity

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